CRITICAL READING SEMINAR

Efficacy of Atenolol and Captopril in Reducing Risk of Macrovascular and Microvascular Complications in Type 2 Diabetes: UKPDS 39

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Introduction

- Focus for this critical reading seminar will be UKPDS 39 (1) (BMJ 1998;317:713-20). Important background contained within UK Prospective Diabetes Study (UKPDS) VIII. Study design, progress and performance. (2) (Diabetologia 1991;34:877-890), and UKPDS 38 (3) (BMJ 1998;317:703-13).
- Why did I chose this article? Type 2 diabetes is a leading cause of morbidity and mortality. UKPDS is an important trial designed to answer important therapeutic questions in these patients. UKPDS 39 appears to contradict other studies in diabetes concerning the use of ACEIs (4).
- I chose to critically review this paper through the eyes of a clinical nephrologist, and to see what information could be applied to our practice.

UKPDS 39 Background

- Introduction section: Summarized findings of UKPDS 38 study showing that tight blood pressure control in type 2 diabetes reduced diabetes related end point, stroke, and microvascular end points. Prior studies suggested that ACEI reduces proteinuria, but insufficient data for clinical complications in type 2 diabetes. ACEI has theoretical advantage in preventing renal complications and CHF. Beta-blockers have advantage in MI and CHF patients.
- Objective: compare results of treatment of hypertension in patients with type 2 diabetes with ACEI captopril and the beta-blocker atenolol on development of clinical complications of diabetes.

UKPDS 39
Methods

- The blood glucose control study started in 1977 with pilot phase of 600 patients at 5 centers. Additional centers in 1982 and 1987.
- GPs referred newly diagnosed type 2 diabetics aged 25-65 to participating centers. Inclusion criteria: a) fasting glucose > 6 mmol/l on 2 mornings, b) willing to participate. Exclusions (28% of referred patients): ketonuria, MI in previous year, current angina or CHF, >1 major vascular event, Scr > 175umol/l, retinopathy needing laser, malignant HTN, uncorrected endocrine abnormality, inability to take insulin, limited life span, unwilling to participate. Treated with diet for 3 months. Patients remaining hyperglycemic (6-15umol/l) without symptoms could continue.
- Subjects for Hypertension in diabetes study (HDS) recruited from glucose study group beginning in 1987 at 20 centers.

UKPDS 39
Patients

- Of 4297 patients recruited to the 20 centers: (fig 1, ref 1)
  - 243 died or lost to f/u prior to start of HDS
  - 2510 not hypertensive (>160/90 on no meds;>150/85 on meds).
- 1544 with HTN. Exclusions: need for strict BP control or beta-blocker, severe vascular disease, concurrent illness or contraindication to beta-blocker, pregnancy, or unwillingness to participate.
  - 252 excluded
  - 144 did not participate
  - 1148 included (727 not previously treated; 421 w/previous treatment)
- 1148 randomized: (baseline characteristics table 1 UKPDS 38)
  - 390 less tight control (<200/105 initially; reduced to <180/105 in 1992)
  - 758 tight control (<150/85) (baseline table 1 UKPDS 39)
    - 400 ACEI
    - 358 beta blocker

UKPDS 39
Methods

- BP measurements: by trained nurse w/patient sitting after 5 min rest. Copal UA-251 or Takeda UA-751 automatic BP machine in non-obese patients. In patients with arm circumference > 33 cm, Hawksley BP machine with large cuff used. Hawksley used in patients w/a-fib. Korotkoff phase 5 used for DBP. 4 readings with 2 min intervals recorded. Average of last 3 readings used for study.
- Randomization (not blinded): computer generated and maintained in sealed envelope by coordinating center.
  - stratified for those with and without prior HTN tx
  - 66.6% to tight control and 33.3% to less tight control
  - balanced numbers in glucose control groups

UKPDS 39
Treatment

- Less tight control group: If treatment goal not met without meds, furosomide, nifedipine, methyldopa, prazocin added sequentially until target met. ACEI and beta-blockers avoided. (unknown # received captopril or atenolol)
- Tight control group: captopril 25 mg bid or atenolol 50 mg qd added. If target not achieved, captopril increased to 50 mg bid or atenolol increased to 100 mg qd. Other meds added in sequence as per less tight control group.

UKPDS 39
Clinical Endpoints

- Predefined primary outcome analyses were the time to the occurrence of:
  - first clinical end point related to diabetes
  - death related to diabetes
  - death from all causes
- Additional clinical end point aggregates to assess effect of tx on vascular disease in secondary outcome analysis:
  - myocardial infarction
  - stroke
  - amputation or death from peripheral vascular disease
  - microvascular complications
- Subclinical surrogate variables:
  - microalbuminuria (>50 mg/l)
  - clinical albuminuria (>300 mg/l)
  - retinopathy and visual acuity

UKPDS 39
Analysis

- Primary analysis on intention to treat basis
- Cox's proportional hazards models used to estimate relative risks.
- 95% confidence intervals used for end point aggregates
- 99% confidence intervals used for single end points and surrogate variables
- RR derived from frequency tables.
- Survival function estimates calculated using Kaplan-Meier method
- Power estimates (table 6, ref 2) calculated for detecting clinically significant advantage between less tight control vs. tight control. No estimation for power between ACEI and beta-blocker

UKPDS 39
Results

- BP control followed for up to 9 years (atenolol vs. captopril): Similar SBP levels. Lower DBP in atenolol group.
- Long-term compliance: better in captopril group
  - more discontinued due to cough in captopril group
  - more discontinued due to claudication, cold feet, and bronchospasm in beta-blocker group.
  - 5 patients in captopril group discontinued due to elevated creatinine. Discontinuation due to elevated creatinine not reported in atenolol group.

UKPDS 39 Results

- Primary outcome measures
  - No difference in clinical end points related to diabetes, diabetic deaths, or all cause deaths
- Secondary outcome measures
  - No differences in MI, stroke, PVD, or microvascular complications
  - “Similar proportions of patients…, progressed to renal failure,..” (# of patients not described or shown).
- Surrogate end points
  - Retinopathy (no difference)
  - Renal failure. Trend toward significance in clinical proteinuria (P=0.090)
  - No difference in plasma creatinine concentrations or twofold increase in creatinine from randomization (data not shown).

UKPDS 39
Results

- Other effects
  - Atenolol treated group had higher glycated hemoglobin over first 4 years
  - Atenolol treated patients required greater glucose lowering treatment
  - Atenolol treated patients gained more weight compared to captopril treated patients

UKPDS 39
Conclusions (as stated by study)

- “BP lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. This study provided no evidence that either drug has any specific benefit or deleterious effect, suggesting that BP reduction in itself may be more important than the treatment used.”

UKPDS 39
McMaster Points

- Is topic interesting: yes
- Is topic relevant in your field of interest: yes; type 2 diabetes is leading cause of ESRD and a large proportion of patients seen in clinic
- Do the authors have a good track record? Very large authorship within UKPDS Group. Main authors have track record publishing in the diabetic field.
- Abstract: offers quick review; type of design clear; results useful
- Introduction: Provided pertinent review and references. Summarized results of UKPDS 38. Developed questions of a) is the benefit of blood pressure lowering in type 2 diabetes due to lower BP or actions of particular BP agent, especially for kidney and heart? Objective of study clear.

UKPDS 39
McMaster Points

- Was the assignment of patients to treatment randomized: yes; method of randomization described.
- Were all clinically relevant outcomes reported? Mortality and diabetic end points related to HTN were reported including retinopathy, stroke, MI, peripheral vascular disease, and renal disease. Markers of renal disease were not carefully reported and were lumped with other microvascular disease outcomes. Non-compliance and side-effects were also reported
- Are there objective and explicit criteria for the clinical outcomes: For most markers there are. Categories of proteinuria described. Markers of renal disease loosely defined in referenced papers and not mentioned in main paper (UKPDS 39), except for proteinuria. Renal outcome results appeared to be lumped with retinopathy for reporting.
- Are observers and subjects blinded to treatment assignments: no

UKPDS 39
McMaster Points

- Are inclusion/exclusion criteria clearly defined and appropriate? Yes
- Are study patients similar to your own? What was the referral pattern for enrolled patients? The study patients have many similarities to those treated in our hospital (referral hospital). The inclusion/exclusion criteria created a patient population that was probably closer to that seen in an internal medicine and endocrinology clinic. Few patients has significant renal disease and therefore were dissimilar to those followed in our nephrology clinic (significant proteinuria, renal insufficiency, and ESRD). Also, the patient population was predominantly white compared to our population which has greater numbers of African-American and Hispanic patients
- Were both statistical and clinical significance considered? Yes
- Were all of the patients who entered the study accounted for by the end of the study? Not clear from UKPDS 39 study. According to UKPDS 38, vital status unknown in 47 patients (?treatment groups)

UKPDS 39
McMaster Points

- Was intention-to-treat analysis used in assessing the data? Yes
- Was the duration of the study follow-up long enough to reach important end-points? This is difficult to answer for all outcomes in UKPDS 39 since it was a “negative” study. Given the minority of patients with signs of renal disease on entry, the duration of study (median 8.4 years follow-up) may have been insufficient to detect “hard” renal outcome data such as death due to renal failure, dialysis, or transplantation. HDS appropriately stopped study when tightly controlled BP found to be superior to less tightly controlled BP. However, there may have been insufficient time to demonstrate that there were no differences between ACEI and beta-blocker.
- Is the therapeutic maneuver feasible in your practice? Yes
- Are these results likely to change your behavior? No.

UKPDS 39 Commentary

- The HDS/UKPDS is a critically important set of trials which demonstrated in type 2 diabetics that a) tight glucose control lowers microvascular complications, and b) tight blood pressure control with a beta-blocker or ACEI reduces diabetic complications and mortality. ACEI captopril was better tolerated than the beta-blocker atenolol, although the clinical significance is uncertain. The trials were carefully designed, analyzed, and reported, especially for important clinical outcomes of importance to primary care providers.
- The conclusion of UKPDS 39 that there were no significant differences between captopril and atenolol appears surprising given growing evidence that ACEIs have advantages for diabetic and non-diabetic renal diseases. The authors specifically cite the Lewis study (4) of ACEI in type 1 diabetics and attempt to explain why methodological errors may have led to results showing superiority of captopril.

UKPDS 39 Commentary

- Although the authors may be correct in their conclusions, what factors could have led the UKPDS 39 to show that there was no advantage to ACEI in preventing significant renal complications?
  - Treatment groups not blinded with potential for bias
  - HDS inadequately designed to specifically test for renal complications. In Lewis study, all patients (n=409) had clinical proteinuria with high risk for renal disease progression. In UKPDS 39 (n=758), 18 patients with clinical proteinuria; 114 with >50 mg/l proteinuria; 117 not tested for proteinuria. Most patients in this study at low risk for renal disease, resulting in inadequate power for studying renal disease.
  - Many patients may have needed longer duration of follow-up to manifest renal complications
  - Atenolol group had lower diastolic BP.
  - Captopril withdrawn in 5 cases due to Scr rise. Authors appropriately mention possibility of renovascular disease. Alternatively, group with elevated Scr had greatest benefit of captopril in Lewis study.

UKPDS 39 Commentary

- (Continued)
  - Precise renal outcome criteria not clearly defined, and lumped with other microvascular complications such as retinopathy.
  - Different dosage regimen: captopril 25 mg bid vs. 25 mg tid in Lewis study
  - Unaccounted patients at end of study
  - Other etiologies for renal disease besides diabetes
- Finally, this study is inadequate to determine that ACEI has no advantage over beta-blocker for preventing renal disease progression in type 2 diabetes.
- Not addressed by this study:
  - Could lower BP target (125/75) produce greater benefit?
  - Do other classes of BP medications have advantages or disadvantages
  - Are there differences among ACEIs, between ACEIs and angiotensin receptor blockers (ARB), or combination ACEI/ARB compared to ACEI or ARB alone?

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